Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Peripheral and Central Nervous System Drugs Advisory Committee Meeting
November 13, 2013

Location: The Sheraton Silver Spring Hotel, Cypress Ballroom, 8777 Georgia Avenue, Silver Spring, Maryland 20910.

Topic: The committee discussed a supplemental Biologics License Application (sBLA) 103948-5139, for alemtuzumab injection, proposed trade name LEMTRADA, submitted by Genzyme Corporation, a Sanofi Company. The proposed indication is for the treatment of patients with relapsing forms of multiple sclerosis to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbations.

These summary minutes for the November 13, 2013, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on January 14, 2014.

I certify that I attended the November 13, 2013, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	***/s/***
Glendolynn S. Johnson, Pharm.D.	Nathan B. Fountain, M.D.
Designated Federal Officer, PCNS	*Chairperson, PCNS*

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
November 13, 2013

The following is final report of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) meeting held on November 13, 2013. A verbatim transcript will be available in approximately six weeks, sent to the Division of Neurology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm346581.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 13, 2013, at the Sheraton Silver Spring Hotel, Cypress Ballroom, 8777 Georgia Avenue, Silver Spring, Maryland 20910. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Genzyme Corporation, a Sanofi Company. The meeting was called to order by Nathan B. Fountain, M.D. (Chairperson); the conflict of interest statement was read into the record by Glendolynn S. Johnson, Pharm.D. (Designated Federal Officer). There were approximately 300 people in attendance. There were ten Open Public Hearing speakers.

Issue: The committee discussed a supplemental Biologics License Application (sBLA) 103948-5139, for alemtuzumab injection, proposed trade name LEMTRADA, submitted by Genzyme Corporation, a Sanofi Company. The proposed indication is for the treatment of patients with relapsing forms of multiple sclerosis to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbations.

Attendance:
PCNS Members Present (Voting): Emilia Bagiella, Ph.D., Robert R. Clancy, M.D., Nathan B. Fountain, M.D. (Chairperson), Richard P. Hoffmann, Pharm.D. (Consumer Representative), Michelle M. Mielke, Ph.D., Paul B. Rosenberg, M.D., Justin A. Zivin, M.D.

PCNS Members Not Present (Voting): Jeffrey A. Cohen, M.D., Ellen J. Marder, M.D., Jason W. Todd, M.D.

PCNS Member Present (Non-Voting): Lynn Kramer, M.D., FAAN (Industry Representative)

Temporary Members (Voting): G. Caleb Alexander, M.D., M.S., Joao Ascensao, M.D., Ph.D., FACP, David E. Blumenthal, M.D., David K. Klassen, M.D., Richard J. Kryscio, Ph.D., Ying Lu, Ph.D., Cynthia Sitcov (Patient Representative), Roy E. Smith, M.D., Mitchell T. Wallin, M.D., M.P.H., T. Mark Woods, Pharm.D., E. Ann Yeh, M.D., FRCPC.

FDA Participants (**Non-Voting):** Ellis Unger, M.D., Eric Bastings, M.D., Billy Dunn, M.D., Evelyn Mentari, M.D., M.S., John R. Marler, M.D.

Designated Federal Officer (Non-Voting): Glendolynn S. Johnson, Pharm.D.

Open Public Hearing Speakers: Douglas G. Franklin (Multiple Sclerosis Association of America), Timothy Coetzee, Ph.D. (National Multiple Sclerosis Society), Carrie Scott, Melissa Burdick, Teresa D. Guess, R.N., David Goldblatt, M.D., Harold C. Johnson, Karen Munley, Amy Love, Maureen Katheryn Russell.

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Nathan Fountain, MD** Chairperson, PCNS
Conflict of Interest Statement	**Glendolynn S. Johnson, PharmD** Designated Federal Officer, PCNS
FDA Introductory Remarks	**Eric Bastings, MD** Acting Director Division of Neurology Products (DNP) Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Genzyme Corporation, a Sanofi Company**
Introduction	**Jennifer Panagoulias, RAC** Senior Director, Regulatory Affairs, Genzyme
Current Medical Needs in MS	**Richard Rudick, MD** Professor of Neurology, Case Western Reserve University Director, Mellen Center for MS Cleveland Clinic Foundation
Pharmacology, Efficacy Data and Analysis of Primary Endpoints from Phase 3 Clinical Program	**David Margolin, MD, PhD** Senior Medical Director, Clinical Research Genzyme **Stephen Lake, ScD** Senior Director, Biostatistics Genzyme **Gary Cutter, PhD** Professor of Biostatistics, School of Public Health University of Alabama at Birmingham **Douglas Arnold, MD** Professor of Neurology, Montreal Neurological Institute McGill University President and CEO, NeuroRx Research Inc.
Integrated Analysis of Safety	**Michael Panzara, MD, MPH** Group VP, Therapeutic Area Head Multiple Sclerosis & Neurology, Genzyme

SPONSOR PRESENTATIONS (CONT.)

Proposed Risk Evaluation and Mitigation Strategy	**Jennifer Panagoulias, RAC** Senior Director, Regulatory Affairs, Genzyme
Overall Summary of Benefit/Risk	**Edward Fox, MD, PhD** Director, Central Texas Neurology Consultants Clinical Assistant Professor of Neurology, University of Texas

Clarifying Questions

BREAK

FDA PRESENTATIONS

Clinical Review of Effectiveness	**John R. Marler, MD** Clinical Reviewer, DNP ODE-I, OND, CDER, FDA
Statistical Review of Alemtuzumab Efficacy	**Sharon Yan, PhD** Statistics Reviewer Division of Biostatistics I, Office of Biostatistics Office of Translational Sciences, CDER, FDA
Clinical Review of Alemtuzumab Safety	**Evelyn Mentari, MD** Clinical Safety Reviewer, DNP ODE-I, OND, CDER, FDA
Alemtuzumab Risk Management Considerations	**Nyedra W. Booker, Pharm.D., M.P.H** Risk Management Analyst Division of Risk Management Office of Medication Error and Risk Management Office of Surveillance and Epidemiology, CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1) Adequate and well-controlled studies include the following characteristics:

   a. A design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.
   b. Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.
   c. Methods of assessment of subjects' response are well-defined and reliable.
   d. An analysis of the results of the study adequate to assess the effects of the drug.

   An adequate and well-controlled study is capable of distinguishing the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.

   VOTE: Are trials 323 and 324 adequate and well-controlled?

   Vote: YES = 6 NO = 11 ABSTAIN = 1

   Committee Discussion: *The majority of the committee agreed that trials 323 and 324 were not well controlled and demonstrated potential for bias. Several committee members who voted "No" commented on the poor design of the trial with one panel member stating that the scientific rationale of the protocol decisions were not clear. Many of the committee members who voted "Yes" conceded that the study design could have been better, but argued the potential benefits beyond the potential for bias and gave support from the European regulatory authority and Lancet journal articles as reasons the trials were acceptable to them. Additional comments from the members who voted "Yes" included the thought that even with the FDA's recommendations and appropriate precautions, it would have been very difficult to prevent complete bias from this type of trial. The committee member who abstained expressed that both sides made compelling arguments. Please see the transcript for details of the committee discussion.*

2) **VOTE:** Has the applicant provided substantial evidence of effectiveness of alemtuzumab for the treatment of patients with relapsing forms of multiple sclerosis?

   a. YES
   b. NO, because the studies are not adequate and well-controlled
   c. NO, because there is not substantial evidence of effectiveness

   Vote: (A) = 12 (B) = 6 (C) = 0

   Committee Discussion: *The majority of the committee agreed that the applicant provided substantial evidence of effectiveness of alemtuzumab for the treatment of patients with relapsing forms of multiple sclerosis. The committee members who voted "Yes" gave the following reasons to support their vote: 1) even with the FDA reanalysis, alemtuzumab was shown not to be worse than the active treatment; 2) based on the data presented, alemtuzumab was shown to be safe and effective, but did not demonstrate its superiority over currently available treatment options for MS; 3) although there was evidence of bias, the*

evidence of effectiveness regarding relapse is substantial; 4)the MRI data also illustrated efficacy even with the variability; 5) it is important to have another treatment option for those patients who are failing on their current therapies The committee members who voted "No" were concerned that the trials were not adequate and well controlled. Please see the transcript for details of the committee discussion.

3) **VOTE:** Has the applicant provided substantial evidence that alemtuzumab has a beneficial effect on disability?

Vote: YES = 2 NO = 14 ABSTAIN = 2

Committee Discussion: *The majority of the committee agreed that the applicant did not provide substantial evidence that alemtuzumab has a beneficial effect on disability. The committee members who voted "No" expressed concerns that the trials were biased, lacked reproducibility and noted the inconsistency between the two study results (trial 323 had a negative result and trial 324 had a positive result). Several panel members stated that they could not vote "Yes" to this question based on positive results from one study. One committee member who voted "Yes" commented that the sponsor made a compelling case to support Sustained Accumulation of Disability (SAD) and the other panel member who voted "Yes" commented that alemtuzumab was proven to be as beneficial as currently available treatment options for MS. The committee member who abstained expressed concerns regarding the inconsistency between the two study results. Please see the transcript for details of the committee discussion.*

4) **VOTE:** In the context of the purported benefits of alemtuzumab, do the safety concerns preclude approval?

Vote: YES = 0 NO = 17 ABSTAIN = 1

Committee Discussion: *The majority of the committee agreed that the safety concerns should not preclude approval. Many of the committee members expressed their opinion that properly informed patients and their physicians could evaluate the benefit-risk profile and determine if alemtuzumab is the best treatment option for their condition. Many panel members also suggested that a proper REMS program and a black box warning will reduce the risk of harmful adverse events. A few panel members expressed their concern that the effects from alemtuzumab are long lasting unlike drugs with a shorter elimination process. Please see the transcript for details of the committee discussion.*

5) **VOTE:** If the available data support approval, should alemtuzumab be indicated as a first-line therapy?

Vote: YES = 0 NO = 16 ABSTAIN = 2

Committee Discussion: *The majority of the committee agreed that alemtuzumab should not be indicated as a first-line therapy. The committee members who voted "No" noted that alemtuzumab is not superior to treatment options currently available for MS. Many of the panel members also expressed concerns regarding alemtuzumab's safety profile compared to*

other treatment options available that have a much lower adverse event profile. One panel member stated that if the evidence was highly robust with the same safety profile, alemtuzumab could then be considered as a first line treatment option. Another panel member conveyed that since alemtuzumab will have a black box warning, it should not be considered first line therapy. The committee members who abstained indicated that there was not enough information to make a decision. Please see the transcript for details of the committee discussion.

6) **DISCUSSION:**

a. Are there any strategies that will mitigate the autoimmune serious adverse events and malignancies given that many of these events occurred after the second course of therapy and with frequent monitoring during the clinical trials?

***Committee Discussion**: The committee suggested that at this time there are no recognized ways to prevent autoimmune adverse events; however, taking corticosteroid injections at the time of alemtuzumab injections would help prevent infusion reactions. Please see the transcript for details of the committee discussion.*

b. Can the Applicant's proposed REMS be modified to ensure adequate monitoring, close follow-up, and reporting of adverse events in patients treated with alemtuzumab, given the proposed dosing regimen and that many of these events occurred after the second course of therapy?

***Committee Discussion**: The committee noted that in addition to a stringent REMS program, the thyroid stimulating hormone (TSH) monitoring should be more frequent. The committee stated that platelet monitoring once a month was sufficient. Please see the transcript for details of the committee discussion.*

c. Discuss the appropriate infusion setting and duration of post-infusion monitoring.

***Committee Discussion**: The committee suggested that alemtuzumab infusion should be conducted in an accredited infusion center. Some panel members expressed concerns for longer monitoring; however, no specific amount of time was suggested. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at 4:56 p.m.